

## Prevention of complications in type 2 diabetes:

is drug glucose control evidence based?

### INTRODUCTION

To answer the questions that arise in relation to a patient's clinical situation, medical decisions need to be made according to the principles of evidence-based medicine. At this time, the benefits and risks of glycaemic control in patients with type 2 diabetes require painstaking reconsideration.<sup>1</sup>

Even if chronic hyperglycaemia is a risk marker for some macro- and microvascular complications, that does not mean *ipso facto* that its reduction by one or several hypoglycaemic drugs is systematically beneficial to patients from a clinical point of view. The potential benefits derived from pharmacological glycaemic control can be counterbalanced by frequent and/or severe clinical adverse events. For example, numerous hypoglycaemic drugs have either not been made commercially available or have been withdrawn from the market in France because their risk-benefit ratio was deemed unfavourable: tolbutamide, phenformin, troglitazone, rosiglitazone, pioglitazone, benfluorex, rimonabant, muraglitazar, and aleglitazar. This was even though they pronouncedly reduced blood glucose level (on average from 0.5% to 2% of HbA1c). The main reason has had less to do with their clinical adverse events than with the lack of evidence of their clinical benefits. Had the efficacy of these drugs been demonstrated in terms of reduced morbidity and/or mortality, they would probably be on the market.

To sum up, the scientific rationale for

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pharmacological treatment of patients with type 2 diabetes depends on the answers to two major questions:

- Is there any evidence derived from randomised controlled trials (RCTs) demonstrating that glycaemic control reduction translates into clinical benefits?
- If yes, do current treatments have a clinically favourable risk-benefit ratio?

### EVIDENCE FROM RCTs ASSESSING INTENSIFIED GLYCAEMIC CONTROL ON MACROVASCULAR COMPLICATIONS

Several RCTs<sup>2-5</sup> have evaluated the intensified glycaemic control strategies targeting an HbA1c level <7%, or even 6% in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,<sup>3</sup> compared with less tight controls (7.5%). These trials were randomised and open intervention, and patients' treatments could vary according to the groups; for example, by using associated drugs with no effect on HbA1c,

but which were effective regarding type 2 diabetes clinical complications.

Taking these limits into account, these trials enabled researchers to come to several conclusions on tight glycaemic control (HbA1c <7%).<sup>6-7</sup>

#### What has been shown

- Tight glycaemic control does not reduce total or cardiovascular mortality.
- It does not reduce the risk of stroke.
- It does not reduce the risk of arteritis or amputation of the lower limbs.
- It does not reduce, and may even increase, the risk of heart failure.

#### What is possible, but requires confirmation

- Intensive glycaemic control reduces the risk of non-fatal myocardial infarction by approximately 15%.
- In one trial,<sup>3</sup> it increased total and cardiovascular mortality, which is a serious warning signal.

**Table 1. Main results of the ACCORD, ADVANCE, and VADT trials**

	ACCORD <sup>3</sup> N= 10 251		ADVANCE <sup>4</sup> N= 11 140		VADT <sup>5</sup> N= 1791	
Δ HbA1c versus control	-1.1%		-0.8%		-1.5%	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Primary outcome	0.90 (0.78 to 1.04) <sup>a</sup>	0.16	0.94 (0.82 to 0.98) <sup>b</sup>	0.01	0.88 (0.74 to 1.05) <sup>c</sup>	0.14
MI + stroke + CV death	0.90 (0.78 to 1.04)	0.16	1.06 (0.94 to 1.16)	0.31	NA	
Death	<b>1.14 (1.01 to 1.46)</b>	<b>0.04</b>	0.93 (0.83 to 1.06)	0.28	1.07 (0.81 to 1.42)	0.62
CV mortality	<b>1.35 (1.04 to 1.76)</b>	<b>0.02</b>	0.93 (0.85 to 1.02)	0.12	1.32 (0.81 to 2.14)	0.26
Non-fatal MI	<b>0.76 (0.62 to 0.92)</b>	<b>0.004</b>	1.02 (0.77 to 1.22)	0.86	0.82 (0.59 to 1.14)	0.24
Non-fatal stroke	1.06 (0.75 to 1.50)	0.74	0.98 (0.76 to 1.15)	NR	0.78 (0.48 to 1.28)	0.32
Severe hypoglycaemia	<b>3.00 (2.55 to 3.54)</b>	<b>&lt;0.0005</b>	<b>1.86 (1.42 to 2.80)</b>	<b>&lt;0.001</b>	<b>3.52 (2.50 to 5.31)</b>	<b>&lt;0.005</b>

<sup>a</sup>MI + stroke + CV death. <sup>b</sup>Major vascular events: MI + stroke + CV death + new or worsening nephropathy (albumin-creatinine ratio >300 µg of albumin per milligram of creatinine or doubling of the serum creatinine level to at least 2.26 mg per decilitre or need for renal-replacement therapy, or death due to renal disease) + retinopathy (development of proliferative retinopathy, or macular oedema or diabetes-related blindness, or the use of retinal photocoagulation therapy). <sup>c</sup>MI + stroke + CV death + heart failure + angina + vascular surgery + amputation. CV = cardiovascular. HR = hazard ratio. MI = myocardial infarction. NR = not reported. Bold = significant.

**Table 2. Results of the meta-analyses of intensive glycaemic control**

	Boussageon <sup>6</sup>	Hemmingsen <sup>7</sup>
Trials, <i>N</i>	13	20
Patients, <i>N</i>	34 533	29 486
Δ HbA1c (%)	0.80	–
Confidence interval	99%	95%
	RR (99% CI)	RR (95% CI)
Overall mortality	1.04 [0.91 to 1.19]	1.01 [0.90 to 1.13]
CV mortality	1.11 [0.86 to 1.43]	1.06 [0.90 to 1.26]
Non-fatal MI <sup>a</sup>	<b>0.85 (0.74 to 0.96)</b>	<b>0.87 (0.76 to 1.00)</b>
Stroke	0.96 [0.83 to 1.13]	0.96 [0.80 to 1.16]
Congestive heart failure	1.17 [0.91 to 1.50]	NR
Nephropathy	<b>0.90 (0.85 to 0.96)<sup>b</sup></b>	0.83 [0.64 to 1.06]
Retinopathy	0.85 [0.71 to 1.03]	<b>0.80 (0.67 to 0.94)<sup>c</sup></b>
Neuropathy	0.99 [0.95 to 1.03]	NR
Severe hypoglycaemia	<b>2.33 (1.62 to 3.36)</b>	<b>2.05 (1.39 to 2.02)</b>

<sup>a</sup>Secondary endpoint. <sup>b</sup>Albuminuria. <sup>c</sup>Composite endpoint. CV = cardiovascular mortality. MI = myocardial infarction. NR = not reported. RR = relative risk. Bold = significant.

These trials (Table 1) support opposing arguments on the causality relationship between drug glucose-lowering control and macrovascular complications related to type 2 diabetes, except perhaps of non-fatal myocardial infarction suggested in some meta-analyses (Table 2). But the benefit on non-fatal infarction is a secondary endpoint, which has been shown only in the ACCORD trial,<sup>3</sup> with a significantly increased total and cardiovascular mortality.

#### EVIDENCE FROM CLINICAL TRIALS INVOLVING INTENSIVE GLYCAEMIC CONTROL ON MICROVASCULAR COMPLICATIONS

- Intensified HbA1c (HbA1c <7%) control could reduce the risk of retinopathy (as evaluated on the Early Treatment of Diabetic Retinopathy Study scale),<sup>7,8</sup> a result shown neither in the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE)<sup>4,9</sup> nor in the Veterans Affairs Diabetes Trial (VADT).<sup>5</sup> However, it does not avoid

photocoagulation,<sup>6</sup> nor does it reduce the risk of loss of vision, or blindness.<sup>6,7</sup>

- It reduces the onset or worsening of nephropathy (assessed on albuminuria).<sup>6</sup> However, it does not prevent a doubling of creatinine level, nor does it reduce the risk of end-stage renal failure or dialysis.<sup>6,7</sup>
- A Cochrane meta-analysis<sup>10</sup> suggests a benefit for neuropathy but does not include the results of the ADVANCE trial.<sup>4</sup> Once that trial is included, it is clear that intensive glycaemic control (HbA1c <7%) does not reduce the risk of onset or worsening of peripheral or autonomic neuropathy.<sup>6</sup>

None of the intensification trials has shown a benefit either on loss of visual acuity or prevention of blindness, which are the most specific and most feared microvascular complications of type 2 diabetes.<sup>6</sup> In the ACCORD trial,<sup>3,8</sup> for example, which reported a difference in HbA1c of 1.1% between groups, moderate loss of vision was not significantly different

(HR = 0.95, *P* = 0.56). In ADVANCE,<sup>4,9</sup> with a difference in HbA1c of 0.8%, and in VADT,<sup>5</sup> with a difference in HbA1c of 1.5%, there was no significant difference regarding the different criteria for retinopathy, particularly visual deterioration.

Finally, it is unclear that the risk–benefit ratio of drug glucose lowering control is favourable. The risk of hypoglycaemia may be higher (two- to tenfold) than the uncertain benefit on retinopathy.<sup>6</sup> In UKPDS-33,<sup>2</sup> in young patients who had been diabetic for 1 year, the absolute risk reduction over 10 years of intensified pharmacological treatment versus diet alone for the ‘microvascular disease’ endpoint was 2.4% (number needed to treat [NNT] = 41) and the absolute increased risk of ‘major hypoglycaemic events’ was 7% (number needed to harm [NNH] = 14) in the glibenclamide-treated group and 11% (NNH = 9) in the insulin-treated group. For older patients who had been diabetic for a longer time period, there is a moderate benefit, but only if applying the therapeutic strategy set in the ACCORD trial,<sup>3,8</sup> with a heightened risk of mortality. A less intensive strategy such as in ADVANCE yielded no benefit for retinopathy but was not associated with higher risk of mortality.<sup>4,9</sup>

#### EVIDENCE FROM DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED CLINICAL TRIALS

To date, none of the available antidiabetic drugs (metformin and insulin included) has clearly and rigorously (superiority trials) proven in the gold-standard double blind RCTs versus placebo to reduce macrovascular or microvascular complications, which are considered as specific to type 2 diabetes.<sup>1</sup>

Even though it is the ‘first line standard treatment’, metformin has not led to reduced microvascular complications in the clinical trials through which it has been tested.<sup>1,11</sup> If one of the main objectives of glucose control is to avoid microvascular complications, it is rather puzzling to have it promoted as a first-line treatment.

#### CONCLUSION

In type 2 diabetes, HbA1c is the biological intermediate criterion for the assessment of diabetic treatments’ efficacy. Thus, any treatment lowering glycemia and HbA1c is defined as ‘antidiabetic’. Such reasoning implies that any reduction in HbA1c is beneficial to the patient. HbA1c is thus considered as a valid criterion for surrogacy. The correlation condition is supported by epidemiological studies

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confirming the statistical association between blood glucose level and the occurrence of macro- and microvascular complications without threshold effect.<sup>12</sup> But this correlation between HbA1c level and diabetic complications observed in epidemiological studies is inter-individual whereas the correlation investigated in meta-regression of RCTs<sup>13</sup> is both inter- and intra-individual and therefore more suitable to support the validity of the surrogate outcome. Ultimately, only RCTs can provide the evidence.

So, the evidence does not support intensive glycaemic control (HbA1c <7%) as the best primary objective in the treatment of patients with type 2 diabetes in terms of reduction of mortality or severe macro- and microvascular complications.

Indeed, none of the major randomised intensification trials has clearly identified one HbA1c target. When the targets have been overly restrictive (as HbA1c <7%), the risk of severe hypoglycaemia and an increased death rate have an unfavourable risk-benefit ratio. However, lower blood sugar is reasonable (although not clearly proven) to prevent metabolic complications or when HbA1c exceeds 9%.<sup>14</sup>

For each patient, it is necessary to measure both the possible benefits of glycaemic control and the risks of potential severe adverse effects associated with antidiabetic drugs. As the risk-benefit ratio of glycaemic control remains uncertain, the benefit-risk ratio of each antidiabetic drug is the key point of the therapeutic decision, independently of its glucose-lowering action. Patients have to be informed about the absence of evidence of the effectiveness of diabetes drugs regarding macro- and microvascular complications, metformin

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and insulin included. With regards to the risk-benefit balance, other treatments for patients with type 2 diabetes (nutrition, physical activity, tobacco cessation, angiotensin-converting-enzyme inhibitors, and statins) should be prescribed as a priority.

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